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# Short-term serotonergic but not noradrenergic antidepressant administration reduces attentional vigilance to threat in healthy volunteers



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## Abstract

Anxiety is associated with threat-related biases in information processing such as heightened attentional vigilance to potential threat. Such biases are an important focus of psychological treatments for anxiety disorders. Selective serotonin reuptake inhibitors (SSRIs) are effective in the treatment of a range of anxiety disorders. The aim of this study was to assess the effect of an SSRI on the processing of threat in healthy volunteers. A selective noradrenergic reuptake inhibitor (SNRI), which is not generally used in the treatment of anxiety, was used as a contrast to assess the specificity of SSRI effects on threat processing. Forty-two healthy volunteers were randomly assigned to 7 d double-blind intervention with the SSRI citalopram (20 mg/d), the SNRI reboxetine (8 mg/d), or placebo. On the final day, attentional and interpretative bias to threat was assessed using the attentional probe and the homograph primed lexical decision tasks. Citalopram reduced attentional vigilance towards fearful faces but did not affect the interpretation of ambiguous homographs as threatening. Reboxetine had no significant effect on either of these measures. Citalopram reduces attentional orienting to threatening stimuli, which is potentially relevant to its clinical use in the treatment of anxiety disorders. This finding supports a growing literature suggesting that an important mechanism through which pharmacological agents may exert their effects on mood is by reversing the cognitive biases that characterize the disorders that they treat. Future studies are needed to clarify the neural mechanisms through which these effects on threat processing are mediated.

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## Introduction

Contemporary cognitive psychology models emphasize the role that biases in threat processing play in the aetiology and maintenance of clinical states of anxiety (e.g. Beck et al., 1985; Eysenck, 1992, 1997; MacLeod et al., 2004; Mogg and Bradley, 1998; Williams et al., 1988, 1997; Yiend and Mackintosh, 2004). Individuals with high trait anxiety and patients with a range of clinical anxiety disorders have been shown to have threat-related biases in selective attention. For example, studies using the attentional probe paradigm

have demonstrated that individuals with high levels of anxiety are relatively faster to respond to probes that replace threatening stimuli than probes that replace neutral stimuli compared with low-anxiety controls, indicating increased attentional vigilance to the location of the threat stimuli (Koster et al., 2005; Mogg et al., 1994, 1997; Yiend and Mathews, 2001). There is also good evidence that interpretative biases favouring threat also play an important role in a wide range of anxiety disorders (e.g. Clark et al., 1997; Eysenck et al., 1991; Huppert et al., 2007; Stoler and McNally, 1991). For example, when presented with a homograph that has both a threat meaning and a non-threat meaning (such as 'patient'), individuals with high levels of trait anxiety and patients with anxiety disorders are typically faster to report whether a word is a real word or a non-word in response to an associate of the threat

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interpretation (e.g. 'hospital') than an associate of the neutral interpretation (e.g. 'calm') compared with low-anxious controls (Richards and French, 1992).

Reducing threat-related processing biases is a major focus of cognitive-behavioural therapeutic interventions for the treatment of anxiety disorders (Beck et al., 1985). Recently, evidence has emerged to suggest that pharmacological treatments for mood disorders may also influence emotional processing. For example, short-term (7 d) administration of the selective serotonin reuptake inhibitor (SSRI), citalopram, and the selective noradrenaline reuptake inhibitor (SNRI), reboxetine, has been shown to reduce the processing of negative emotional material, such as fearful and angry faces, and to increase the perception of and memory for positively valenced emotional material in healthy volunteers (Harmer et al., 2004). Importantly, these changes in emotional processing occur in the absence of significant differences in subjective mood and more rapidly than the therapeutic effects of these drugs would typically be seen clinically. This suggests that antidepressants may directly modulate the neural processing of emotional and social information, rectifying the maladaptive processing biases seen in depression. This may represent an important mechanism by which these pharmacological agents exert their therapeutic effects.

Given the growing evidence of the therapeutic value of SSRIs in the treatment of a range of anxiety disorders (Dhillon et al., 2006; Kent et al., 1998; Pae and Patkar, 2007), an outstanding question is whether SSRIs have effects on emotional processing biases that are particularly relevant to anxiety. There is some evidence from clinical studies to support this notion. For example, Mogg and colleagues (2004) reported that patients with generalized anxiety disorder produced significantly fewer threat-related spellings of homophones following 4 wk treatment with a SSRI compared to before treatment. Furthermore, this reduction in threat-related interpretative bias was positively correlated with clinical improvement, suggesting that it was relevant to the therapeutic action of the drug. The major difficulty with interpreting such effects, however, is that it is not possible to distinguish the direct action of the drug on threat processing from non-specific effects of symptom change produced by the SSRI treatment. Assessment of the cognitive effects of short-term antidepressant administration to healthy volunteers is one method of circumventing this problem, as it allows the direct effect of the drug to be assessed in the absence of symptom change and in comparison with a placebo control group. The current study therefore assessed the effect of a SSRI on

anxiety-related emotional processing paradigms in healthy volunteers.

Unlike SSRIs, selective noradrenaline reuptake inhibitors (SNRIs), while effective antidepressants, are not commonly used in the treatment of anxiety. Consistent with this, we have previously reported that whilst both of these classes of antidepressants positively bias emotional processing, they have a different profile of effects on response to threat as measured by the emotion-potentiated startle response (Harmer et al., 2004). Thus, while 7 d citalopram administration reduces the potentiation of the startle response by negative pictures in healthy volunteers, reboxetine has no effect on this paradigm (Harmer et al., 2004). On the basis of this, we have previously hypothesized that whilst citalopram influences emotional processing biases that are relevant to both anxiety and depression, the effect of reboxetine is expressed more specifically on the elaborative and explicit processes that are particularly implicated in depression. In order to test this hypothesis, a reboxetine-treated group was included in the present study as an additional contrast.

The current study therefore assessed the effect of 7 d treatment with the SSRI, citalopram, and the SNRI, reboxetine, on anxiety-related threat processing paradigms in healthy volunteers. This treatment period was chosen because, as mentioned above, 7 d administration of antidepressants to healthy volunteers has previously been shown to have significant effects on emotional processing (Harmer et al., 2004). A 7-d treatment period also has the particular advantage of allowing the effects of the drug on emotional processing to be measured before the full therapeutic effect would typically be seen in clinical populations. Threat processing was assessed with a commonly used test of attentional vigilance to threat (the attentional probe task, using emotional facial expressions as stimuli) and a commonly used test of interpretative bias (the homograph primed lexical decision task). It was predicted that citalopram would reduce attentional and interpretative threat-relevant biases compared with placebo but that reboxetine would have no effect on these anxiety-related emotional processing paradigms.

## Methods

A total of 42 (20 male, 22 female) volunteers took part in the study. Participants were recruited through adverts in University departments and screened to exclude those with a current or previous history of psychiatric disorder [assessed using the Structured Clinical Interview for DSM-IV (SCID)]; history of alcohol or other substance abuse or dependence

**Table 1.** Demographic characteristics of 42 healthy volunteers randomly assigned to 7 d intervention with citalopram, reboxetine or placebo. There were no significant differences between the three groups on any of these measures

	Placebo		Citalopram		Reboxetine	
	Females	Males	Females	Males	Females	Males
Total in group	( <i>n</i> = 8)	( <i>n</i> = 6)	( <i>n</i> = 8)	( <i>n</i> = 6)	( <i>n</i> = 7)	( <i>n</i> = 7)
Age (yr)	25.75 (5.3)	23 (1.7)	23.1 (3.1)	25.3 (2.5)	24.9 (2.4)	23.4 (2.1)
Verbal IQ	117.6 (4.8)	120.1 (5.8)	114.4 (3.8)	118 (6.0)	116.4 (3.5)	120.7 (3.7)

Values represent the mean with the standard deviation in parentheses.

(assessed using SCID criteria); pregnancy or lactation; history of significant medical disorder; and current usage of any medication other than oral contraception. Four (three citalopram group, one reboxetine group) of the participants were occasional smokers (defined as <2 cigarettes per day). All participants gave their written informed consent to participate in the study, which was approved by Oxfordshire Research Ethics Committee in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Volunteers were randomly allocated to double-blind intervention with one of the three following oral treatments for a period of 7 d: placebo, citalopram (20 mg/d) or reboxetine (4 mg b.i.d.). Medication was given in identical capsules twice a day to maintain blinding. The three groups were matched in terms of gender, verbal IQ (assessed with the National Adult Reading Test) and age (see Table 1). Participants were asked to refrain from drinking alcohol during the study week and were not allowed to drink caffeine or smoke during the test session on day 7. Testing did not take place during female participants' premenstrual week.

Subjective mood was recorded before and on day 7 of treatment using the following questionnaires: State-Trait Anxiety Inventory (Spielberger et al., 1983), Buss-Durkee Hostility Inventory (Buss and Durkee, 1957), Dysfunctional Attitudes Scale (Weisman and Beck, 1978). On day 7 of intervention, participants completed the attentional probe task and the homograph primed lexical decision task.

#### Attentional probe task

Pairs of photographs of 20 individuals were taken from the JACFEE/JACNeuF sets of facial expressions

(Matsumoto and Ekman, 1988). Each face pair comprised one emotional and one neutral expression of the same individual or two neutral expressions of the same individual. Half of the emotional faces were fearful and half were happy. Thus, there were three types of face pairs: neutral-neutral, fearful-neutral and happy-neutral. On each trial, one of the faces appeared above and the other below the central fixation position. The task was fully counterbalanced for emotion location, probe location and probe type. In the unmasked condition, the face pair was presented for 100 ms and was immediately followed by a probe, which appeared in the location of one of the preceding faces. The probe was two dots presented either vertically (:) or horizontally (:). Participants were required to report the orientation of the dots by pressing a labelled key on a keyboard. The dots remained on the screen until participants had made their response. Participants were asked to respond as quickly and as accurately as possible. The sequence of events was the same in the masked condition, except the face pair was displayed for 16 ms and followed by a mask (constructed from a jumbled face), which was displayed for 84 ms.

The timing of the masked and unmasked condition was decided based upon the results of a pilot study. It was important to identify timings that produced attentional vigilance effects to the fearful faces in healthy, low anxious volunteers, in order to be able to investigate whether citalopram reduces such vigilance. In the pilot study, eight healthy, unmedicated volunteers completed a masked and unmasked version of the task, each with two timing conditions (masked: 16 ms target, 84 ms mask and 16 ms target, 234 ms mask; unmasked: 100 ms target and 250 ms target). Consistent with a previous study using angry faces in a dot probe paradigm (Cooper and Langton, 2006), the 100-ms unmasked condition produced significant attentional vigilance effects towards the fearful faces compared with neutral, whereas there was no significant attentional vigilance to the fearful faces in the 250-ms target unmasked condition. Similarly, the shorter of the two masked timing conditions (16 ms target, 84 ms mask) but not the longer produced significant attentional vigilance effects towards the fearful faces.

There were 192 trials in total (masked: 32 happy-neutral, 32 fear-neutral, 32 neutral-neutral; unmasked: 32 happy-neutral, 32 fear-neutral, 32 neutral-neutral). There were eight blocks of unmasked trials (12 trials per block) and eight blocks of masked trials (12 trials per block) which were presented in an alternating order with an ABAB design.

Trials with response times of  $\leq 100$  ms, or  $\geq 2000$  ms were excluded from the analysis. The mean percentage of data lost due to reaction time outliers was 0.16%. Attentional vigilance scores were calculated for each participant by subtracting the mean reaction time from trials when probes appeared in the same position as the emotional word (congruent trials) from trials when probes appeared in the opposite position to the emotional word (incongruent trials). Positive values reflect attention towards the emotional face (vigilance) and negative values reflect attention away from the emotional face (avoidance).

#### *Threat/neutral homograph and lexical decision making task*

Eighty threat/neutral homographs were selected from the norms compiled by French and Richards (1992) to be used as primes. Each homograph had two primary meanings, which differed significantly in threat value, as rated by 12 independent judges (see French and Richards, 1992 for details). For each homograph, a word associated with the threat meaning and a word associated with the neutral meaning was selected to be used as the related targets. These were generally the most common word associated with each meaning, however, occasionally an alternative word was selected in order to avoid repetition and to help matching. Each prime was also paired with a semantically unrelated target from both the threat set and the neutral set. This procedure was carried out by one experimenter (K.L.) and independently verified by a second experimenter (S.M.). The neutral and threat targets were matched for word length and association strength. Forty of the homograph primes were used in word trials and the other half were used on non-word trials with a set assignment that was counterbalanced across participants. The procedure for creating the non-word pairings was the same as described above with the addition of an extra step in which one of the letters of each of the target words was changed in order to produce a pronounceable non-word. Each homograph was only presented once and followed by a non-word target (40 trials) or one of four possible word targets: related neutral target (10 trials), related threat target (10 trials), unrelated neutral target (10 trials), unrelated threat target (10 trials).

On each trial, a fixation cross was presented for 2 s, followed by a homograph prime which was presented in lower-case letters in the middle of the screen for 750 ms. Immediately following the prime, the word or non-word target was displayed in upper-case letters on the screen and participants were required to press

one of two keys on the keyboard to indicate whether the word was a legitimate English word or not. The target remained on the screen until volunteers had made their response and the timing of responses began with the presentation of the target. Participants completed four practice trials prior to the experimental trials in order to familiarize themselves with the task procedure. There was an untimed rest period halfway through the task in order to minimize fatigue.

#### *Statistical analyses*

Data were analysed using split-plot two-way analyses of variance (ANOVAs). For all ANOVAs, treatment group (citalopram, reboxetine or placebo) was the between-subjects factor. The within-subjects factors were: emotion and time (subjective mood scales); face valence and masking (attentional probe task); target valence and trial type (homograph task). Gender was also initially entered as a between-subjects factor. However, if the main effect of gender and interactions of gender and treatment group were found to be non-significant, data were collapsed across gender for subsequent analyses. Where necessary, the interpretation of significant effects was aided by the use of simple main-effect analyses. Where assumptions of equality of variances were broken, the Greenhouse-Geisser procedure was used to correct the degrees of freedom.

#### *Results*

##### *Subjective mood, anxiety and hostility*

There were no significant effects of treatment group on any of the measures of subjective mood, anxiety or hostility (see Table 2).

##### *Attentional probe task*

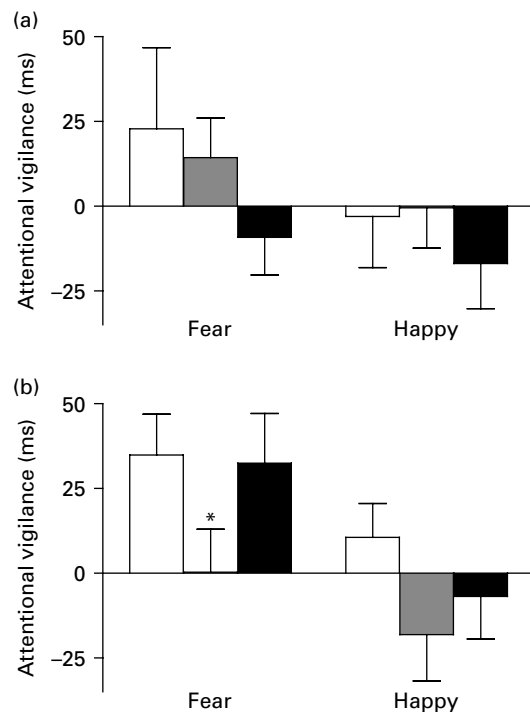
Accuracy rates were very high in this task (placebo, mean 94%; citalopram, mean 92%; reboxetine, mean 92%) and there were no significant effects of treatment group on accuracy across any of the task conditions (all comparisons,  $p > 0.2$ ). Data from trials with errors were therefore discarded and not analysed further. There was no significant effect of treatment group on average overall reaction times or on reaction times on the neutral-neutral trials (all  $p$  values  $> 0.2$ ), suggesting no baseline reaction time differences between the three groups. An ANOVA was performed on the attentional vigilance scores with two between-subjects factors (treatment group and gender) and two within-subjects factors (face valence and masking). This

**Table 2.** Subjective state ratings before and after 7 d treatment with placebo, citalopram or reboxetine. There were no significant effects of treatment group on any of the measures

Measure	Score											
	Placebo ( <i>n</i> = 14)				Citalopram ( <i>n</i> = 14)				Reboxetine ( <i>n</i> = 14)			
	Before treatment		After treatment		Before treatment		After treatment		Before treatment		After treatment	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
State-Trait Anxiety Inventory												
State Anxiety	31.5	7.4	32.6	10.6	32.9	8	32	9.8	31.5	7.3	29	6.28
Trait Anxiety	32.4	7	34	10.1	33.1	6.7	33.6	7.2	29	4.8	29.7	5.6
Buss–Durkee Hostility Inventory	22.5	5.7	21.1	6.6	24.9	5.4	25.6	7.5	23.8	11.6	23.4	11.5
Dysfunctional Attitudes Scale	114.6	22.8	113.2	27.1	128.2	24.8	130.4	25.1	114.4	33.3	114	30.1

Values represent mean and standard deviation (S.D.).

revealed a significant main effect of valence [ $F(1,36) = 4.797$ ,  $p = 0.035$ ], which reflected significantly greater attentional vigilance towards the fearful faces than the happy faces. There was no significant three-way interaction between group  $\times$  valence  $\times$  masking status. However, there was a significant interaction between group and masking status [ $F(2,36) = 4.402$ ,  $p = 0.019$ ]. In order to investigate this in more detail, attentional vigilance in each masking condition was analysed separately. In the masked condition there were no significant effects of valence or group on attentional vigilance (all  $p$  values  $> 0.2$ ). However, in the unmasked condition, there was again a significant effect of valence [ $F(1,39) = 7.312$ ,  $p = 0.01$ ] reflecting relatively greater attentional bias to the fearful faces than the happy faces across all groups (see Figure 1). There was also a significant main effect of group [ $F(2,39) = 3.704$ ,  $p = 0.03$ ]. Post-hoc least significant difference comparisons revealed that significant differences between the placebo and the citalopram group ( $p = 0.02$ ) and between the citalopram and reboxetine groups ( $p = 0.03$ ) were driving this main effect. There was no significant difference between the placebo and reboxetine groups ( $p = 0.9$ ). It can be seen from Figure 1 that these differences were mainly driven by a decrease in attentional vigilance to fearful faces in the citalopram group compared with the placebo and reboxetine groups. Group differences on attentional vigilance measures do not indicate which of the groups is exhibiting an absolute bias (see Gotlib et al., 1988). To clarify this, one-sample  $t$  tests were used to compare attentional bias scores to zero within each group. These analyses revealed that the placebo and



**Figure 1.** Attentional vigilance in the attentional probe task in (a) the masked condition and (b) the unmasked condition. Vigilance is calculated by subtracting mean reaction time to respond when probe replaces emotional face (fearful or happy) from the reaction time when the probe replaces the neutral face. Thus the higher the vigilance score, the greater the attentional bias towards the emotional face. Error bars represent standard error of mean (\*  $p < 0.05$  for comparison between citalopram and placebo groups and between reboxetine and citalopram groups). □, Placebo; ■, citalopram; ■, reboxetine.

**Table 3.** Reaction times for threat and neutral targets following the presentation of a threat/neutral homograph prime in the homograph primed lexical decision task

Threat/neutral prime	Placebo	Citalopram	Reboxetine
Threat target			
Related (R)	649.8 (46.9)	632.5 (32)	654.3 (41.9)
Unrelated (U)	773.5 (72.2)	732.7 (61.5)	742.3 (47.6)
Difference U–R	+123.7 (39.3)	+100.2 (32.5)	+88 (41.6)
Neutral target			
Related (R)	648 (42.6)	679 (47.5)	645.6 (35.8)
Unrelated (U)	728.2 (47.5)	720.5 (50)	702.8 (44.3)
Difference U–R	+80.3 (17.4)	+41.5 (16.8)	+57.2 (26.3)

Values represent mean with standard error of the mean in parentheses.

reboxetine groups both showed a significant bias towards fearful faces [placebo:  $t(13)=2.502$ ,  $p=0.027$ ; reboxetine:  $t(13)=2.218$ ,  $p=0.045$ ]. In contrast, the citalopram group showed no significant bias to fearful faces [ $t(13)=0.023$ ,  $p=0.982$ ]. None of the three treatment groups showed a significant bias towards happy faces (all  $p$  values  $>0.1$ ). Attentional vigilance scores on this task were not significantly affected by gender and there were no significant interactions between gender and treatment group (all  $p$  values  $>0.09$ ).

#### *Homograph primed lexical decision task*

Data from one volunteer (citalopram group) is missing due to technical difficulties. There was no significant effect of treatment group on accuracy in this task [ $F(1,38)=0.363$ ,  $p=0.7$ ] and no significant interaction between target valence and treatment group [ $F(2,38)=0.405$ ,  $p=0.670$ ]. Trials with errors were therefore discarded and not included in any further analyses. An ANOVA was performed on the mean reaction times for correct responses to word targets presented following threat/neutral primes. This analysis had two between-subjects factors (treatment group and gender) and two within-subjects factors; target valence (threat vs. neutral) and target type (related vs. unrelated). This revealed a significant main effect of target type [ $F(1,36)=28.83$ ,  $p<0.001$ ] and a significant interaction between target valence and target type [ $F(1,36)=4.96$ ,  $p=0.032$ ]. As can be seen from Table 3, across all treatment groups and both target valences, volunteers were significantly faster to respond to targets that were related to the prime compared to targets that were unrelated to the prime. This facilitation effect was

more pronounced for threat than neutral targets. However, there were no significant effects of treatment group on this pattern ( $p>0.2$  for all comparisons). Reaction times on this task were not significantly affected by gender and there were no significant interactions between gender and treatment group (all  $p$  values  $>0.1$ ).

#### **Discussion**

This study examined the effect of 7 d treatment with two different classes of antidepressant drugs on threat processing in healthy volunteers. The findings suggest that short-term administration of the SSRI citalopram reduces attentional vigilance towards emotional faces but does not affect the interpretation of ambiguous homographs as threatening. As predicted, the SNRI, reboxetine, did not have any significant effects on either of these measures of biases in the processing of threat.

#### *Citalopram and attentional vigilance to emotional faces*

Citalopram administration reduced attentional vigilance to emotional faces independently from valence, reflected in a significant main effect of treatment group on the attentional probe paradigm. Further analyses suggested that this effect was primarily driven by reduced attentional vigilance to fearful faces. Whilst both the placebo group and the reboxetine group showed a significant bias towards fearful faces, this was abolished in the citalopram group. There is a considerable body of empirical data demonstrating heightened attentional vigilance towards threatening stimuli in individuals with high levels of trait anxiety and individuals with a range of clinical anxiety disorders (Koster et al., 2005; MacLeod et al., 1986; Mogg and Bradley, 2002; Yiend and Mathews, 2001). It has been suggested that these cognitive biases may play an important role in the maintenance, and possibly even the underlying aetiology, of anxiety (e.g. MacLeod et al., 2002, 2004; Mathews and MacLeod, 1994; Yiend and Mackintosh, 2004). Such biases are a major focus of cognitive behavioural therapy for anxiety disorders and there is evidence that threat-related cognitive biases are reduced following successful psychological intervention (e.g. Mathews et al., 1995). The present study suggests that SSRIs may similarly act to reduce attentional biases towards threat through a pharmacological mechanism. Furthermore, given that these effects were seen in healthy volunteers in the absence of any significant changes in mood or anxiety,

the current findings suggest that reduced attentional vigilance to threatening environmental stimuli may represent a direct effect of serotonergic antidepressant administration, seen relatively early in treatment, and which may be relevant to the therapeutic actions of this pharmacological agent.

Several models suggest that anxiety biases attention towards threat-related stimuli by increasing the output from an amygdala-centred threat evaluation system (Mathews and Mackintosh, 1998; Öhman and Wiens, 2004). This hypothesis is supported by a range of neuroimaging studies indicating hyperarousal of the amygdala in anxiety disorders both at rest and in response to threat-relevant stimuli (Birbaumer et al., 1998; Liberzon et al., 1999; Mathews et al., 2004; Rauch et al., 1996, 2000; Semple et al., 2000; Shin et al., 1997). Such a proposal is also consistent with evidence from animal and human studies suggesting that the amygdala is critically involved in the fast, automatic appraisal of threat stimuli and directing attention towards emotionally salient, biologically relevant events (Davis and Whalen, 2001; LeDoux, 1995). In line with the dense serotonergic innervation of the amygdala, it seems reasonable to suggest that the SSRI effects on attentional vigilance to threat seen in the present study may be mediated through interactions with this circuitry. In support of this notion, 7 d administration of citalopram to healthy volunteers has recently been shown to reduce the amygdala response to masked presentations of fearful faces (Harmer et al., 2006).

There is a growing body of evidence to suggest that the attentional biases in threat processing seen in anxiety do not necessarily depend on conscious awareness of the emotional stimuli. For example, in an attentional probe paradigm anxious individuals have been shown to orient to the position of previously presented threat-related stimuli, even when they were backwardly masked and therefore presented below the level of conscious awareness (Mogg et al., 1995b). Such preconscious attentional biases to threat have been shown to be reduced following cognitive behavioural therapy (e.g. Mogg et al., 1995a). However, contrary to predictions, there was no significant effect of citalopram on attentional vigilance to masked fearful faces in the present study. There are two potential methodological limitations in the task design that may have contributed to this lack of effect. First, the attentional vigilance to the fearful faces in the placebo group was less marked in the masked condition compared to the unmasked condition and therefore the power to detect a modulation of this bias in the citalopram group may have been insufficient. Second, no assessment of awareness of the masked stimuli was

carried out. The threshold for the detection of backwardly masked stimuli has been shown to be dependent on a number of factors, including the particular discrimination task used and individual differences. For example, Mogg and Bradley (1999) note that if stimuli are presented very close to awareness thresholds, the pre-attentive effects of masked stimuli may be reduced. Therefore, any degree of variability between the treatment groups in the present study in terms of the threshold for awareness of the masked stimuli may have confounded the effect of the drug treatment on attentional vigilance to these stimuli.

It should be noted that it is difficult to draw any conclusions about the effect of citalopram on attentional vigilance to happy faces from the present study, since there was no significant bias effect in the placebo group. The primary aim of the present study was to examine the effect of citalopram on selective attention to threat-related stimuli and the timings of the attentional probe paradigm were therefore selected (on the basis of pilot data) to ensure a robust attentional bias towards fearful faces in the placebo group. Consistent with a previous report using angry faces, it was found that a short stimulus presentation time of 100 ms produced a robust attentional vigilance effect towards threat-related face stimuli in healthy volunteers (Cooper and Langton, 2006). It may be, however, that attentional vigilance towards positive stimuli is better studied using longer stimulus presentation times. In support of this, Cooper and Langton (2006) report opposite patterns of vigilance and avoidance for happy and angry faces across presentation times. They report a bias towards angry faces at 100 ms followed by a significant bias away from angry faces at 500 ms. Conversely, they found a significant bias away from the happy faces at 100 ms and a bias towards happy faces at 500 ms. Further studies are needed to investigate the effects of antidepressants on the processing of positively valenced emotional material and how this may differ from threat-related processing.

#### *Citalopram and threat-related interpretative biases*

Contrary to predictions, we found no effect of citalopram on the interpretation of ambiguous homographs. All three treatment groups showed faster responses to targets that were related to the homograph primes, indicating that the priming was effective. In addition, the three groups all showed a relatively increased priming effect for the threat-related primes compared with the neutral-related primes, suggesting a threat-related interpretative bias that was not modulated by



antidepressant treatment. The lack of effect of citalopram on this task contrasts with a previous report of reduced threat-related spellings of homophones following 4 wk citalopram treatment in a group of patients with generalized anxiety disorder (Mogg et al., 2004). This previous study did not have a placebo control group so it is possible that the post-treatment reduction in threat-related interpretative bias reflects practice effects rather than a specific effect of the drug on interpretation. A more interesting explanation for the divergent findings relates to the longer SSRI treatment period (4 wk) used in the previous study compared to the present study (1 wk). Whilst the early effects of SSRIs may relate specifically to selective attention to threat, over time it is possible that they may generalize to influence a broader spectrum of emotional and social processing. Future studies are needed to assess how the effects of antidepressants on emotional processing change with repeated administration.

#### *Reboxetine and threat processing*

As predicted, the noradrenergic antidepressant reboxetine did not significantly affect attentional vigilance to threat or the threat-related interpretation of ambiguous homographs. This is consistent with a previous study in which both citalopram and reboxetine were shown to enhance the processing of positive vs. negative information on a number of tasks that tapped into processes relevant to the cognitive biases seen in depression (such as emotional memory and the recognition of facial expressions) but only citalopram modulated responses on the emotion-potentiated startle task, a paradigm known to be particularly relevant to fear and anxiety processes (Harmer et al., 2004). A lack of effect of reboxetine on attentional vigilance to threat-related stimuli is also in line with the limited clinical usage of this drug in the treatment of anxiety compared with citalopram. Indeed, UK guidelines on the treatment of anxiety disorders recommend pharmacological treatment with SSRIs and tricyclic antidepressants, but do not recommend treatment with SNRIs, such as reboxetine (NICE, 2007). Such concordance between the effects of these drugs on specific emotional processes and their clinical usage lends further support to the therapeutic relevance of the neuropsychological effects seen. It should be noted, however, that there is some evidence that reboxetine is effective in the treatment of some anxiety disorders, in particular panic disorder, and this distinction is therefore not absolute (e.g. Seedat et al., 2003; Versiani et al., 2002).

#### *The use of healthy volunteers*

Studying the mechanisms of antidepressant drugs in healthy volunteers has the advantage that the behavioural effects of the drugs can be explored unfounded by changes in clinical state or symptom remission. Consistent with our previous studies, we found no significant effect of citalopram or reboxetine on mood or subjective state, as measured by self-report scales (Harmer et al., 2003a,b, 2004). This suggests that the observed changes following drug administration represent direct effects of the drugs on emotional and threat processing rather than a secondary consequence of mood improvement. However, it is important to note that the participants used in this study were generally young, high-functioning students. Whilst the homogeneity of this sample has the advantage of increasing the power to detect drug-related differences between treatment groups, this restricted demographic profile is not typical of the whole spectrum of depressed and anxious clinical populations. Clearly it is necessary to assess whether similar effects occur following drug treatment in depressed and anxious patients and whether such early effects on emotional processing are predictive of eventual therapeutic efficacy.

#### *Limitations*

There are a number of limitations to the present study that must be considered. First, we did not have a physiological measure of compliance with the drug treatment. However, the significant effects of citalopram on emotional processing make it likely that there was good compliance with the treatment in, at least, the majority of participants. Second, the use of a between-subjects design has the disadvantage of variability across the treatment groups generated by individual differences. A cross-over design was not used in this study because of the considerable order effects that can be seen in emotional processing paradigms. Indeed, data from our laboratory has consistently indicated that the effects of antidepressants on emotional processing are strongest on the first test session (C. Harmer, unpublished observations). Consistent with this, it is well established that the habituation of neural responses to repeated exposure to stimuli is particularly pronounced in response to stimuli with an emotional valence. In particular, a range of studies have demonstrated that the amygdala rapidly habituates to repeated presentations of emotional faces (Breiter et al., 1996; Whalen et al., 1998; Wright et al., 2001) and pictures (Fischer et al., 2000; Irwin et al., 1996). Animal studies using the

acoustic startle response as an indirect measure of amygdala function suggest that such habituation effects are not just seen within sessions but can also persist across testing sessions (e.g. Stevenson and Gratton, 2004). For this reason, all of the participants in this study were naive to the experimental stimuli used. However, the between-subjects design did necessitate careful matching of the groups on a range of factors (such as age, gender, baseline subjective mood ratings) in order to ensure internal validity. Finally, SSRIs are known to have complex interactions with a number of different neurotransmitter systems, including the noradrenergic and dopaminergic systems. It is therefore not possible to conclude that the effects of citalopram on threat processing seen in the present study are directly mediated by an increase in serotonin.

## Conclusions

In summary, the present study demonstrated that citalopram reduces attentional orienting to threatening stimuli, which is highly relevant to its clinical use in the treatment of anxiety disorders. This finding supports a growing literature suggesting that an important mechanism through which pharmacological agents may exert their effects on mood is by reversing the cognitive biases that characterize the disorders that they treat. Future studies are needed to clarify the neural mechanisms through which these effects on threat processing are mediated.

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## Statement of Interest

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